REMARKS

I. Status of Claims:

Upon entry of the instant amendment claims 1, 6, 8, and 13-32 will be pending in this application, claims 2-5, 7 and 9-12 having been previously canceled and claims 29-32 newly added. Claims 13-21 are withdrawn as drawn to a non-elected invention. Support for new claims 29-32 can be found, for example, at page 14, lines 1-4. Claims 1 and 28 have been amended herein. Support for the amendments can be found, for example, at page 15, lines 13-30. No new matter is added. Applicants ask that the new claims, all of which depend from claim 1 or claim 28, be examined with the presently elected group.

II. Amendments to the Specification:

The specification has been amended to correct minor clerical errors. No new matter is added.

III. Rejections Under 35 U.S.C. § 103(a):

Claims 1, 6, 8, and 22-28 are rejected as allegedly being obvious over Ridgway *et al.* (*Protein Engineering*, 9:617-621 (1996)) ("Ridgway") in view of Peipp *et al.* (*Biochemical Society Transactions*, 30:507-511 (2002)) ("Peipp") and Shalaby *et al.* (*J. Experimental Medicine*, 175:217-225 (1992)) ("Shalaby"). *See*, Office Action at pages 3-7. Applicants traverse.

In rejecting claims under 35 U.S.C. § 103, the Patent Office bears the initial burden of presenting a *prima facie* case of obviousness. *In re Oetiker*, 977 F.2d 1443, 1445 (Fed.Cir.1992). Only if that burden is met does the burden of coming forward with evidence or argument shift to the applicant. *Id.* To establish a *prima facie* case of obviousness, the Patent Office must : (i) show that the prior art teaches each of the claimed elements; and (ii) explicitly describe "an apparent reason to combine the known elements in the fashion claimed," *KSR Int'l*

Co. v. Teleflex, Inc., 550 U.S. 398 (2007). As explained in detail below, Applicants respectfully submit that the Patent Office has not set forth a proper *prima facie* case of obviousness.

Applicants' claims are directed generally to methods of producing four-chain, bispecific antibodies by expressing all four different chains of the bispecific antibody in the same cell. A typical antibody is composed of two arms – each arm consisting of a heavy chain and a light chain. In "monospecific" antibodies, the two arms are identical and thus both arms bind identical epitopes. The two arms of "bispecific" antibodies, however, are different, permitting the bispecific antibody to bind two different epitopes. Bispecific antibodies are more difficult to produce, compared to monospecific antibodies, because expression of four different chains (two kinds of light chains and two kinds of heavy chains) in the same cell can lead to the four chains' randomly assembling into 10 different possible species. Of these 10 species, only one species is the desired bispecific antibody having one copy of each of the four different chains, and with the proper pairing between light and heavy chains. Applicants' invention provides a novel method of producing a desired bispecific antibody following expression of all four chains of the antibody in a single cell. The method involves inducing expression of the two chains of one arm of the bispecific antibody, ceasing induction of expression of the two chains of the first arm, and then inducing expression of the two chains of the second arm. When the heavy and light chains of the first arm are expressed in the cell, they will pair up together, because there is only one kind of light chain and one kind of heavy chain present in the cell and available for pairing. After induction of expression of those two chains ceases, most if not all of the expressed chains of the first arm will be paired up and unavailable for pairing with any subsequently expressed chains. At that point, expression of the heavy and light chains of the second arm is induced. When the heavy and light chains of the second arm are expressed, they pair with each other because there are no, or at least relatively few, heavy and light chains of the first arm available for pairing. In sum, temporal expression of the chains of the first and second arms solves the problem of random mispairing of the two heavy and two light chains of the bispecific antibody into 10 different arrangements. The first and second arms of the bispecific antibody can then be heterodimerized using any technique known in the art (*e.g.*, "knobs-into-holes" engineering).

None of the cited references either alone or in combination teaches Applicants' claimed invention.

The Office Action alleges that Ridgway was successful in co-expressing two light chains and two heavy chains in the same cell. Applicants disagree with the Office Action's interpretation of Ridgway. Ridgway co-transfected phagemids encoding one anti-CD3 heavy chain, one anti-CD3 light chain and a CD4-IgG fusion polypeptide into cells to produce heterodimers, each of which had three (not four) chains: one antibody heavy chain, one antibody light chain, and one CD4-IgG chain. CD4-IgG is neither an antibody heavy chain nor an antibody light chain; rather, CD4-IgG is a recombinant fusion of soluble CD4 (not an antibody chain) and the Fc portion of immunoglobulin G (i.e., a portion of a heavy chain). Thus, contrary to the assertion in the Office Action of October 23, 2007, Ridgway does not "describe a process for producing a bispecific antibody having an Fc region, wherein the H chain and L chain which constitute a first set have a [*sic*] antigen recognition site and the H and L chain which constitute a second pair have another antigen recognition site . . ." (*see*, Office Action, page 3; emphasis supplied). What the Examiner apparently believes is the "second pair" of Ridgway's heterodimer is actually a single hybrid polypeptide chain having an Fc region and no antigen recognition site. Ridgway does suggest that the T366Y and Y407T knobs-into-holes mutations used to induce binding of the anti-CD3 antibody arm with the Fc region of the CD4-IgG fusion polypeptide may have applicability in Fc-containing bispecific antibodies. Specifically, Ridgway states:

> The T366Y and Y407T mutations are directly applicable to the construction of bispecific IA, which further expand IA as a class of novel therapeutic. In addition, the mutations identified are anticipated to increase the clinical potential of Fc-containing BsAb by reducing the complexity of the mixture of products obtained from a possible 10 major species down to four or less. (see, page 620, right column, fourth full paragraph, references omitted).

In other words, Ridgway was able to create heterodimers by the "knobs-into-holes" engineering design strategy, and predicted that this technique, if applied to bispecific antibodies, would reduce the number of random mispairings that occur in the cell from "10 major species down to four or less." Ridgway's reference to "four or less" species reflects his recognition that the problem of mispairing of a light chain with the incorrect heavy chain is not solved by the knobs-

into-holes technique. Ridgway simply avoided this problem in his own experiments by using only one kind of light chain and one kind of heavy chain, and having the CD4 IgG fusion polypeptide serve as the second arm.

Shalaby teaches the production of a bispecific $F(ab')_2$ consisting of an arm that has specificity toward the extracellular domain of $p185^{HER2}$ and an arm that has specificity toward the human T cell surface marker CD3. Shalaby avoids the mispairing of the four chains of the bispecific $F(ab')_2$ by expressing each arm separately, in different cultures of cells, followed by purification of each arm from the cells in which it was expressed, chemical modification of one of the arms to make it reactive, and finally directed chemical coupling of the two arms to each other. See the carryover paragraph of pages 218-219. Nowhere in Shalaby is there any teaching, suggestion or motivation to express both arms (i.e., all four chains) of the bispecific antibody in the same cell. In fact, doing so would have produced the 10 different random arrangements mixed together, the problem that Shalaby was trying to solve by producing the arms separately (i.e., in separate cultures) and linking them chemically. Shalaby's technique for solving the problem is thus entirely different from Applicants' method.

Peipp is a review article that discusses bispecific antibodies. Figure 1 of Peipp provides, among others, a schematic representation of a bispecific antibody format that is referred to as "knobs-into-holes." Although this diagram shows a bispecific antibody having two different arms, Applicants note that this diagram must be considered in the context of Peipp's disclosure. Outside this figure, the only other mention of knobs-into holes is a brief description of a technology described in a review article by Paul Carter (*see*, page 510, left column, first incomplete paragraph). The method described in Carter uses the knobs-into-holes engineering to create heavy chain heterodimers and then "to completely circumvent the L chain mispairing problem" used "antibodies with identical L chains that bind to different antigens by virtue of their distinct H chains." (*see*, Carter, page 10, right column, first full paragraph and Figure1B, C; emphasis added). Thus, considered in context, Peipp's knobs-into-holes bispecific antibody in Figure 1 actually corresponds to Carter's knobs-into-holes heavy chains paired with identical light chains. No other way to produce knobs-into-holes bispecific antibodies with proper heavy-

light chain pairing is suggested in Peipp or Carter. Nowhere in Peipp or Carter is there any teaching or motivation whatsoever of Applicants' claimed method.

According to the Office action at page 4, "There is no requirement [in Ridgway] that the proteins would necessarily be expressed at the same time absent a showing by Applicants to the contrary." The Office action cites no reason why it would have been obvious to separate the time of expression of the two arms of a heterodimer, as required by the present claims, other than the lack of a "requirement" in Ridgway. Applicants submit that this is not the proper analysis. Even if Ridgway does not disclose a "requirement" that the anti-CD3 heavy and light chains "necessarily be expressed at the same time" as the CD4-IgG fusion polypeptide, it is clear that Ridgway does not disclose (nor even suggest) that they may be expressed at different times. Nor could one read into Ridgway any possible reason to separate expression temporally. It would have served no purpose, given the facts of Ridgway, to express one arm of the heterodimer at a time distinct from the period in which the second arm is expressed. It is the Examiner's burden to show why the art taught it would have been obvious to express the two arms at separate times, and not the Applicants' burden to show why there was a "requirement" in Ridgway to express them at the same time. The Examiner has not even posited a reason one of ordinary skill, upon reading Ridgway, might have wanted to express the two arms at separate times, much less established that it would have been obvious to do so. Accordingly, Applicants submit that the Examiner has not met her burden, and the obviousness rejection fails.

Rather than teaching a temporally separated expression of the two arms in order to control proper pairing of light and heavy chains, the approaches taught in the cited art to overcome the mispairing of the light and heavy chains include:

(1) using a single, Fc-containing fusion polypeptide (CD4-IgG) as the second arm instead of using a heavy chain associated with a light chain as the second arm (Ridgway);

(2) expressing the antigen binding fragments (Fab') of two different antibodies in separate cells and chemically coupling the purified Fab' fragments to form a heterodimer (Shalaby); and

(3) using identical light chains (Peipp/Carter).

The Office Action has provided no evidence or reasoning that the combined teachings of the cited art would motivate the ordinary artisan to discard all three of the methods used by the three references to avoid mispairing of antibody chains, and instead substitute an entirely different method taught in none of the references: differentially timed expression in the same cell.

For the foregoing reasons, Applicants respectfully assert that the Patent Office has not established a *prima facie* case of obviousness and therefore request that this rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

IV. Rejections Under 35 U.S.C. § 112, First Paragraph, Enablement:

Claims 1, 6, 8, 22, 23, 27, and 28 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Office Action alleges that the specification does not provide enablement for inducing "just any kind of cell" to express a first light chain and a first heavy chain at one time and to express a second light chain and a second heavy chain at a different time under "just any conditions." *See*, Office Action at pages 7-10.

To overcome this rejection, the Action suggested amending independent claims 1 and 28 to recite, in relevant part, that the eukaryotic cell is recombinant and vector transformed. *See*, Office Action at page 10.

Applicants have amended independent claims 1 and 28 to recite, in relevant part, that the eukaryotic cell is recombinant and that the DNAs or nucleic acids encoding the heavy and light chains are exogenous. Applicants respectfully submit that this amendment is sufficient to overcome the outstanding enablement rejection. Accordingly, Applicants request that this rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

V. Rejections Under 35 U.S.C. § 101:

Claims 1, 6, 8, 22, 23, 27, and 28 are rejected under 35 U.S.C. § 101 for allegedly being inoperative and therefore lacking utility. The Examiner states that there has been no demonstration of an individual B cell or any eukaryotic cell undergoing site-specific

recombination for two different antibodies within the same cell. *See*, Office Action at pages 10-13.

Independent claims 1 and 28 have been amended to specify that the eukaryotic host cell is recombinant and that the DNAs or nucleic acids encoding the heavy and light chains are exogenous. Thus, the claims are not directed to "any eukaryotic cell undergoing site-specific recombination for two different antibodies within the same cell." Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 101 be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully submit that all claims are now in condition for allowance and accordingly request the timely issuance of a Notice of Allowance.

If the Examiner would like to discuss this application, she is invited to call the undersigned at the telephone number provided below.

Applicants petition for a three-month extension of time to respond to the outstanding Office Action. Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14875-0154US1.

Respectfully submitted,

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/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
Customer No. 26161
Telephone: (617) 542-5070
Facsimile: (877) 769-7945